

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Baker et al.
Serial No. : 827,187 Art Unit: 1203
Filed : January 28, 1992 Examiner: Celia Chang
For : IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES

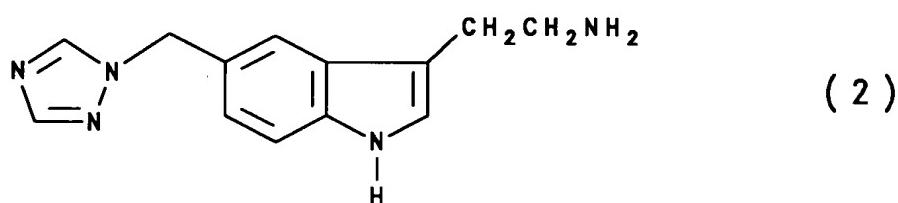
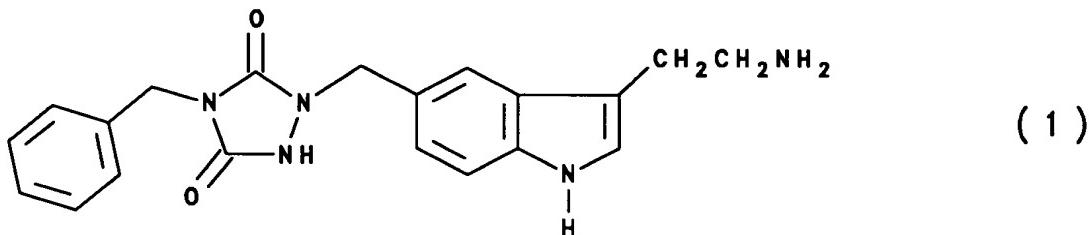
Commissioner of Patents and Trademarks
Washington, D.C. 20231

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DECLARATION UNDER RULE 132

I, LESLIE JOSEPH STREET, declare as follows:

1. I have obtained the degrees of Bachelor of Science and Doctor of Philosophy from the University of Leeds, United Kingdom. My present position is Senior Research Fellow in the Department of Medicinal Chemistry at Merck Sharp and Dohme Research Laboratories (MSDRL), England, and I have been employed by MSDRL since October, 1985. I have been responsible, in the normal course of my duties, for synthesizing various imidazole, triazole and tetrazole derivatives with a view to ascertaining their activity as agonists of so-called 5-HT₁-like receptors and hence their likely benefit in the treatment of clinical conditions, particularly migraine, requiring this activity.
2. I am a co-inventor of the subject-matter described and claimed in the subject patent application. I have read published European Patent Application no. 0313397, which relates to a class of tryptamine derivatives substituted by a five-membered heteroaliphatic ring.
3. At my instigation, tests were carried out in order to compare the binding affinity for 5-HT₁-like receptors of the following compounds:



Compound (1) is the title compound of Example 24 of published European Patent Application No. 0313397. Compound (2) is the title compound of Example 5, Step 4 of the subject application.

4. In carrying out the said tests, the standard assay described in J. Neurosci., 1987, 7, 894 was employed. Binding of test compounds to 5-HT₁-like receptors was determined in membranes prepared from pig caudate using 2 nM 5-hydroxytryptamine creatinine sulphate, 5-[1,2-³H(N)], as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively.

5. The results obtained from the said tests were as displayed in the following Table:

Compound	IC ₅₀ (μ M)
(1)	6.31
(2)	0.05

6. With reference to the above Table, the parameter IC₅₀ is a measure of the ease with which a given test compound is capable of displacing the radioligand from binding sites pre-labelled therewith. Thus, since IC₅₀ is expressed in terms of the concentration of test compound required to displace 50% of the specific binding, it follows that a lower value of IC₅₀ indicates a more potent compound.

7. The results displayed in the above Table demonstrate a clear advantage for the compounds of the subject application relative to those of published European Patent Application no. 0313397. Thus, compound (2) can be observed to be >120 times more potent at binding to 5-HT₁-like receptors than compound (1). This significant improvement in activity could not have been predicted from the disclosure of published European Patent Application no. 0313397.

8. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. I am also aware that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

Leslie Street
LESLIE JOSEPH STREET

Date:

January 11th 1993